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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,129	06/19/2003	Sarah S. Bacus	02-434-A	9778

7590 01/26/2009

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
01/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/600,129	BACUS ET AL.
	Examiner	**Art Unit**
	ANNE L. HOLLERAN	1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *1-28 and 35-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Claims 1-38 are pending. Claims 1-28 and 35-38, drawn to non-elected inventions, are withdrawn from consideration. Claims 29-34 are pending and examined on the merits.

Claim Rejections Withdrawn:

Claim Objections

The objection to claim 29 for using the abbreviation "OD" with first spelling out the term in its entirety is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 112-second paragraph

The rejection of claims 30, 32 and 34 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicants' persuasive argument.

Claim Rejections - 35 USC § 112-first paragraph

The rejection of claims 29-34 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating subjects having renal cancer comprising first selecting the patient population by detecting levels of HER3, where the cut-off for selection is an OD less than 9 as determined by quantitative immunohistochemistry, does not reasonably provide enablement for treating a subject with any type cancer comprising first selecting a patient population using the method recited in the claims and the cut-off for selection recited in the claims is withdrawn upon further consideration.

New Grounds of Rejection:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 29, 31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak (US 5,770,195; issued Jun. 23, 1998) in view of Esteva (Esteva, F. J. et al., Pathology Oncology Research, 7(3): 171-177, 2001), in view of Pinkas-Kramarski (Pinkas-Kramarski, R. et al, Oncogene, 16: 1249-1258, 1998), and further in view of Hoffmann (Hoffmann, M., et al., Cancer Immunol. Immunother., 47(3): 167-175, 1998; abstract only). This is a new grounds of rejection because Pinkas-Kramarski and Hoffmann are cited in addition to Hudziak, and Esteva.

The claimed methods comprise two active steps: that of assaying for the expression level of HER3 in cells from a cancer and the second step of treating the subject with an EGFR

antibody if the HER3 expression levels detected have an OD less than 9 when determined by quantitative immunohistochemistry that the subject is treated.

Hudziak teaches and claims a method of treating cancer that expresses EGF receptor with an anti-EGFR antibody (see claims 14-33). Hudziak fails to teach a patient selection step of first measuring levels of Her3 in a sample from a patient.

Esteva teaches measuring levels of EGFR, Her-2, Her-3, Her-4, heregulin, P-p38 (phosphorylated p38), P-MAPK(phosphorylated MAPK) and P-Her-2 (phosphorylated Her-2). For Her-3, Esteva teaches that a median OD level of 0.85 is the cutpoint to discriminate between high and low levels. MAPK is a synonym for Erk (see Database PIR, Accession No. P28482 (MK01_Human, Georgetown University, Washington, DC, Version 95, 2/26/2008). Esteva teaches that tumors that express HER-3 and HER-4 exhibit cellular growth and drug resistance and that HER-3 and HER-4 have been shown to be receptors to other growth factors (such as EGF an EGFR growth factor, see reference #41 and page 176, first column). Esteva also teaches that identification of marker associated with the biological and clinical behavior of breast cancer may eventually be useful to predict a tumors response to adjuvant chemotherapy (see page 175).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Esteva to measure levels of HER-3 prior to treating a patient with an anti-EGFR antibody because Esteva teaches that HER-3 is known to be associated with insensitivity to chemotherapeutic agents and because HER-3 is known to be activated by ligands for other HER receptors, such as EGF and betacellulin. Furthermore, Pinkas-Kramarski teaches that the ErbB-2/ErbB-3 (Her-2/Her-3) heterodimer forms a binding site for ligands such as EGF and betacellulin, which induce proliferative signals (see page 1251).

Additionally, Hoffmann teaches that expression of receptors such as ErbB-3 and ErbB-3 are associated with TNF-alpha insensitivity. Therefore, one would have been motivated by the teachings of Esteva that HER-3 levels are associated with insensitivity to chemotherapeutic agents, the teachings of Pinkas-Kramarski that ErbB-2/ErbB3 heterodimers bind to and produce proliferation signals from EGFR ligands such as EGF and betacellulin, and the teachings of Hoffmann that Her-2 and Her-3 are associated with TNF-alpha insensitivity, to screen patients for expression of Her-3 to better select patients that would respond to an anti-EGFR antibody such as that anti-EGFR antibody of Hudzizk. Hudziak teaches combining anti-EGFR antibodies with a second therapeutic, TNF-alpha, and also with cytotoxic agents. .

Applicants have argued that Esteva fails to cure the deficiencies of Hudziak in that Hudziak fails to teach a prior selection step of measuring levels of Her-3. Applicants state that Esteva does not teach or suggest that nay of these patterns of expression and /or activation can be used to select a subject with cancer for treatment with a molecule targeting EGFR, and that Esteva does not teach treating a subject with an anti-EGFR antibody. Applicants also argue that the claims do not require the use of multiple chemotherapeutic agents with an anti-EGFR antibody, and state that it does not follow that just because expression of Her3 might correlate with an insensitivity to chemotherapeutic agents in general that low expression of Her3 would necessarily result in sensitivity to non-specific chemotherapeutic agents, or to sensitivity to anti-EGFR antibodies. Applicants' arguments have been carefully considered, but fail to persuade, because the claims are not limited to methods of treatment consisting of solely the administration of an EGFR antibody, but instead encompass methods such as that in Hudziak where an anti-EGFR antibody is combined with an agent such as TNF-alpha, or other cytotoxic agents.

Furthermore, Esteva, Pinkas-Kramarski, and Hoffmann provide evidence that at the time of filing it was known that ErbB3 transmitted growth signals in cancers, in addition to evidence that ErbB3 expression correlated with insensitivity to chemotherapeutic agents or to TNF-alpha. Therefore, in a method to treat cancer by targeting EGFR, one would be motivated to avoid treating cancers that possessed a second growth signal pathway, such as cancers that expressed Her3. Applicants state that the Office has not provided any legitimate reason why it would have been predictable to the skilled artisan that Her3 would be a negative predictor of a response to an anti-EGFR antibody. However, in view of the newly provided references, this is not found persuasive, because the prior art demonstrates that EGFR ligands stimulate growth of cancer cells via Her-3. Thus, in tumors with both EGFR and Her3 providing growth signals it is reasonable to expect that inhibition of only EGFR might be a less effective therapy than if the anti-EGFR therapy was provided to a tumor with only EGFR signaling to provide a growth signal to the tumor.

Claims 29-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak (US 5,770,195; issued Jun. 23, 1998) in view of Esteva (Esteva, F. J. et al., Pathology Oncology Research, 7(3): 171-177, 2001), in view of Pinkas-Kramarski (Pinkas-Kramarski, R. et al, Oncogene, 16: 1249-1258, 1998), in view of Hoffmann (Hoffmann, M., et al., Cancer Immunol. Immunother., 47(3): 167-175, 1998; abstract only), and further in view of Yang (Yang, X.-D. et al., Critical Reviews in Oncology/Hematology, 38: 17-23, 2001). This is a new grounds of rejection because Pinkas-Kramarski and Hoffmann are cited in addition to Hudziak, Esteva and Yang.

The claimed methods comprise two active steps: that of assaying for the expression level of HER3 in cells from a cancer and the second step of treating the subject with an EGFR antibody if the HER3 expression levels detected have an OD less than 9 when determined by quantitative immunohistochemistry that the subject is treated. The claims encompass the use of antibody that is encompassed by the term "ABX-0303".

Hudziak, Esteva, Pinkas-Kramarski and Hoffmann teach as set forth above. Hudziak, Esteva, Pinkas-Kramarski and Hoffman fail to teach the ABX-0303 antibody.

However, ABX-0303 appears to be a useful anti-EGFR antibody, because Yang teaches that it is a completely human antibody, and because it completely eradicates a human tumor xenograft (see page 20, section 2.3). Also, Yang teaches that the antibody appears to be useful in xenografts that express high levels of EGFR. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used Yang's ABX-EGF antibody in Hudziak's method of treating EGFR-expressing cancers. One would have been motivated by the teachings of Yang with regard to efficacy of the ABX-EGF antibody and also because the ABX-EGF antibody is a fully human antibody that would be expected to be less immunogenic.

Applicants have argued that Yang, taken alone or in any combination with Hudziak and Esteva do not reach or suggest the claimed methods because Yang does not overcome the deficiencies of Hudziak and Yang, and Yang does not teach or suggest that Her3 can be used as a biomarker for the use of ABX-0303. Applicants' arguments have been carefully considered, but fail to persuade. The claims are not limited to methods of treatment consisting of solely the administration of an EGFR antibody, but instead encompass methods such as that in Hudziak

where an anti-EGFR antibody is combined with an agent such as TNF-alpha, or other cytotoxic agents. Furthermore, Esteva, Pinkas-Kramarski, and Hoffmann provide evidence that at the time of filing it was known that ErbB3 transmitted growth signals in cancers, in addition to evidence that ErbB3 expression correlated with insensitivity to chemotherapeutic agents or to TNF-alpha. Therefore, in a method to treat cancer by targeting EGFR, one would be motivated to avoid treating cancers that possessed a second growth signal pathway, such as cancers that expressed Her3. Applicants state that the Office has not provided any legitimate reason why it would have been predictable to the skilled artisan that Her3 would be a negative predictor of a response to an anti-EGFR antibody. However, in view of the newly provided references, this is not found persuasive, because the prior art demonstrates that EGFR ligands stimulate growth of cancer cells via Her-3. Thus, in tumors with both EGFR and Her3 providing growth signals it is reasonable to expect that inhibition of only EGFR might be a less effective therapy than if the anti-EGFR therapy was provided to a tumor with only EGFR signaling to provide a growth signal to the tumor.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry

Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
January 20, 2009
/Alana M. Harris, Ph.D./
Primary Examiner, Art Unit 1643